JAPAN

Examining the first biosimilar patent litigation

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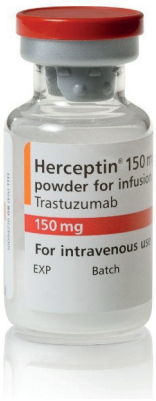

The direction of drug discovery has moved from focusing on low molecular weight compounds to biopharmaceuticals, and the percentage of biopharmaceuticals being sold is increasing. The first biosimilar patent litigation was also filed.

Summary of the case

According to the press releases of Chugai Pharmaceutical and Nippon Kayaku, as well as others, the facts are as follows.

Genentech is the owner of a patent entitled "Dosages for treatment with anti-ErbB2 antibodies" (JP5818545), and Chugai is an exclusive licensee of the patent.

Claim 1 of the patent is as follows.

Claim 1

(i) A container containing a pharmaceutical composition for the treatment of breast cancer characterised by overexpression of HER 2, the pharmaceutical composition containing an anti-ErbB2 antibody huMab4D5-8, the treatment comprising administering to the patient by intravenous injection an initial dose of 8mg/kg of the antibody followed by two or more subsequent doses of 6mg/kg of the antibody, wherein the subsequent doses are separated in time from each other by at least three weeks and

(ii) a package comprising a package insert associated with the container.

On August 17 2017, regarding an anti-HER2 humanised monoclonal antibody "HERCEPTIN® Intravenous Infusion 60" and "HERCEPTIN® Intravenous Infusion 150", Genentech and Chugai filed a lawsuit seeking an injunction on manufacturing and selling etc. of the biosimilar and also filed a petition for a preliminary injunction at the Tokyo District Court on the basis of infringement of the patent right against Nippon Kayaku, who was applying for manufacture and sales approval of the biosimilar.

"HERCEPTIN® Intravenous Infusion" is an antineoplastic drug containing an anti-HER2 humanised monoclonal antibody "Trastuzumab (Genetical Recombination)" as an active ingredient, which was developed by Genentech.

In Japan, effectiveness and efficacy have been observed in breast cancer where overexpression of HER 2 was seen and in unresectable advanced or recurrent gastric cancer where overexpression of HER 2 was observed.

On October 2 2017, Genentech and Chugai withdrew a petition for the preliminary injunction.

On March 19 2018, trial examination was concluded and the judgement date was designated as May 30 2018.

On April 10 2018, Genentech and Chugai waived the claim.

On April 11 2018, Chugai issued a press release saying that it confirmed that the product developed by Nippon Kayaku received a marketing approval for the indication of "unresectable advanced or recurrent gastric cancer where overexpression of HER2 was observed" on March 23 2018. As a result, Chugai judged that the initial purpose of the lawsuit was achieved, and took the procedure for waiver off its claims on April 10.

Practical tips

Biosimilars are expected to save medical expenses. The Basic Policies for Economic and Fiscal Management and Reform 2017 declared that their aim was to achieve a doubling in the number of items based on biosimilars by the end of the fiscal year 2020, while the Basic Policies for the Economic and Fiscal Management and Reform 2018 sought to promote research and development and its diffusion by obtaining understanding of the efficiency and safety of biosimilars. In recent years, formulary has been introduced and is required in medical institutions.

In this case, a lawsuit was filed before Nippon Kayaku obtained a marketing approval for the manufacture and sale of biosimilars, which attracted public attention. It is usual for the original drug manufacturers to file a lawsuit after approval, since they do not know whether generic drug manufacturers have applied for marketing approval. In this case, since Nippon Kayaku issued a press release on April 11 2017 about the application for the marketing approval, Genentech and Chugai came to know of the fact.

In an approval review, misalignment in ineffectiveness and efficacy between an original drug and biosimilar was discussed. The minutes for the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) Second Committee on Drugs, held on February 2 2018 note that Dr Okuda, acting director, made a remark as follows:

"I assume that the approved target disease is out of place. I mean that clinical trial was conducted first of all against the patients of "breast cancer", however, the approval was made for "gastric cancer". Since the reason was described, I thought I had understood it is because the patent was related. I assume that there are many breast cancer patients requiring the drug. If the clinical trial itself has been conducted, is there any information concerning a future view about the indication for breast cancer?"

In answer to this remark, the Pharmaceuticals and Medical Devices Agency (PMDA) replied as follows:

"Since we have heard that at this moment a patent lawsuit is ongoing between the

applicant and Chugai/Genentech, the original drug manufacturers, I am concerned about when the approval will be obtained. I assume that since the associated company of Chugai possesses the patent related to breast cancer, the timing of obtaining effectiveness and efficacy for breast cancer will vary depending on whether or not there is a conflict with the patent."

The above argument shows that the existence of a use patent had an impact on the approval on the specific effectiveness and efficacy.

As the biosimilars of Herceptin, the following are listed: Nippon Kayaku's product, Daiichi Sankyo's product and Pfizer's product. Daiichi Sankyo's product and Pfizer's product received a marketing approval on September 21 2018. The indication of the biosimilar of Nippon Kayaku is only for gastric cancer. On the other hand, the indication of the biosimilars of Daiichi Sankyo and Pfizer includes breast cancer in addition to gastric cancer. However, in the dosage and administration for breast cancer, method B is not employed, where the administration after the second time is performed with three week intervals, a method for the original drug, but only method A is employed, where the administration is performed with a one week interval. Sachiko Masuda, associate professor at the University of Tokyo, pointed out that it is necessary to watch the impact of skinny labelling on the medical front. On October 12 2018, Genentech and Chugai filed a lawsuit against Daiichi Sankyo and Pfizer.

Since judgment was not rendered in this case, a decision regarding infringement and validity concerning biosimilars must be left to another time. As the second biosimilar patent litigation, regarding an anti-CD20 monoclonal antibody, "RITUXAN® Injection 10mg/mL", Genentech filed a patent infringement lawsuit and a petition for preliminary injunction at the Tokyo District Court on December 28 2017, against Sandoz, a manufacturer of a biosimilar of the same product, and Kyowa Hakko Kirin, a distributor. Attention must be paid to the judgment.

As works illustrating the very first story of Herceptin, Robert Bazell's book entitled *HER-2- The Making of Herceptin, a Revolutionary Treatment for Breast Cancer,* and a film titled *Living Proof* are known. They portray the raw truth of the project's crisis, of a breast cancer activist seeking humanitarian use of the drug before FDA approval for patients with an advanced disease, and of an anguished principal investigator.